Gearhart Testimony

Testimony on Stem Cell Science: The Foundation for Future Cures

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Mr. Chairman and Members of the Subcommittee, I am John Gearhart, a stem cell biologist at Johns Hopkins Medicine. I am pleased to appear before you to discuss the foundation for future cures through stem cell science.

It is rare that a field of scientific research can have both an enormous potential impact of human health and quality of life and be a fount of new basic research discovery. What crystallized the scientific and medical communities' interest in stem cell research was the derivation of human embryonic stem cell lines. These cell lines are unique in that they are capable of forming all the different cell types (>220) that are present in the body (a property that is referred to as pluripotentiality) and they can produce more cells like themselves indefinitely (self-renew). This development, first reported ten years ago, has been among the most heralded as well as contentious issues of the modern scientific era. Heralded, as now we had in the laboratory a source of cells from which we could grow any and all cells of the human body for much needed replacement therapies and contentious, because embryos are destroyed to derive the cells. No wonder that stem cell research has impacted many areas of our society – science, medicine, religion, ethics, policy and economics. Seldom has a week gone by without some new revelation about stem cells reaching the front pages of the press or the top news stories of the day and what this means for our society, invariably hyped. It is recognized that stem cell research has the potential to revolutionize the practice of medicine and to improve the quality of life and in some cases, the length of life for many people suffering from devastating illnesses and injuries. Also, it is believed by many that there will be no realm of medicine that will not be impacted by stem cell research.

Research over the past ten years is setting the foundation for the use of embryonic stem cells and the knowledge derived from this research for developing and designing therapies, therapies that will be safe as well as effective. To envision what lies ahead for

the use of these cells in human therapies, it is informative to mention the progress that has been made over the past decade while keeping in mind that the progress made by US investigators has been compromised by current policy on federal funding. In the very first Congressional hearing on these stem cells (December 2, 1998, Before the Senate Appropriations Committee, Subcommittee on Labor, Health and Human Services, Education and Related Agencies) and one in which I had participated, Harold Varmus, MD, then the Director of the National Institutes of Health (now the President of the Memorial Sloan-Kettering Cancer Center) outlined the potential uses of these cells in biomedicine and it is appropriate to use his list in evaluating what has transpired in laboratories since then.

(Varmus) At the most fundamental level, pluripotent stem cells could help us to understand the complex events that occur during human development. A primary goal of this work would be the most basic kind of research -- the identification of the factors involved in the cellular decision-making process that determines cell specialization. We know that turning genes on and off is central to this process, but we do not know much about these "decision-making" genes or what turns them on or off. Some of our most serious diseases, like cancer, are due to abnormal cell differentiation and growth. A deeper understanding of normal cell processes will allow us to further delineate the fundamental errors that cause these deadly illnesses.

There is no question that we have learned a great deal about these stem cells and the molecular mechanisms underlying the bases of pluripotentiality and of cell differentiation, that is, the conversion of these cells into one of the types of specialized cells of the body. This is what we call basic science, a prerequisite first step in understanding cellular processes. We have utilized studies of other organisms to first give us insight into these mechanisms and then confirmed these mechanisms or variations on these mechanisms in the human cells. Much of our progress has been informed by such studies and as has been pointed out recently by Bruce Alberts, Ph.D., there are no shortcuts to medical progress: *But, as has been repeatedly demonstrated, the shortest path to medical breakthroughs may not come from a direct attack against a specific disease. Critical medical insights frequently arise from attempts to understand fundamental mechanisms in organisms that are much easier to study than humans; in particular, from studies of bacteria, yeasts, insects, plants, and worms. For this reason, an overemphasis on "translational" biomedical research (which focuses on a particular disease) would be counterproductive, even for those who care only about disease prevention and cures. (Bruce Alberts, Shortcuts to Medical Progress? Science Vol 319, 28 March 2008).* Embryonic stem cells provide another link in the biomedical investigation and discovery chain that leads to human application.

So, we now know a handful of the critical genes and of the regulation of the expression of these genes that enable cells to be pluripotential. This knowledge was at the basis of the most recent and exciting development in our field in which skin cells were converted to cells that had properties of embryonic stem cells by the addition of just a few genes to the cells. The skin cells had these genes but they were not being expressed. Adding exogenous version genes that were expressed caused these cells to be reprogrammed,

eventually expressing their own, endogenous genes. The embryonic stem cell-like cells are called induced pluripotent stem (iPS) cells. This is a major paradigm shift in stem cell biology and I will comment more on this later but it was through the study of embryonic stem cells that this advance was made.

There have now been hundreds of research reports on studies of in which embryonic stem cells are differentiating to specialized cells. We are learning the mechanisms involved in the earliest decisions made by cells to become neurons or gut cells or muscle cells, etc. It has been know for decades that cell-cell interactions in the embryo determine the fates of cells during development as summarized by the Noble laureate Hans Spemann (1943): *We are standing and walking with parts of our body which we could have used for thinking if they had been developed in another position in the embryo.* With these embryonic stem cells in culture, we are learning how different factors influence cell fate decisions. By experimentally manipulating these factors we can then direct cell differentiation to a desired cell type through the use of growth factors, attempting to mimic the environment of the embryo.

Personally, I have been interested in human embryology and development for decades and have felt strongly as Samuel Taylor Coleridge (1934) stated so beautifully: *The history of man for the nine months preceding his birth would probably be far more interesting and contain events of far greater moment, than all the three-score and ten years that follow.* These stem cells have provided a unique resource to learn about the biologic mechanisms underlying our development, both normal and abnormal, so that we may eventually understand the basis of birth defects and perhaps guide us in correcting these malformations, etc. We have learned much about the mechanisms of cell decision making in the early embryo, such as within the conceptus, becoming embryonic or extra-embryonic, and within the germ layers of the embryo, what determines cell fate. In our own current work with embryonic stem cells, we have recently discovered ~40 new genes that are critical to the formation of the heart and great vessels. There are many other examples for the use of these important cells in studying human development.

Recent findings have discovered and solidified the understanding that many of the same cellular mechanisms found in the development of a tissue or organ play critical roles when rebuilding or regenerating that tissue. Investigators have gone on to show that manipulation of these developmental factors, the understanding for which has been often discovered, expanded and/or validated in embryonic stem cells, can greatly influence regenerative capacity, even recovering the capacity to regenerate in animals that did not possess it. It is of the outmost importance that studies continue in order to discover these and utilize this knowledge in designing therapies for the many maladies affecting us. As all of you have observed, we humans don't regenerated body parts like some of our lower relatives in the animal kingdom. Imagine the possibility of harnessing the capacity of zebrafish, for example, who using the same families of genes that we use in the development of our heart can regrow a large part of their heart when amputated. We must determine the reasons why humans fail to display this capacity in most organs, emboldened by the knowledge that our livers can regenerate, in order to combat many common debilitating diseases such as heart attacks and strokes.

(Varmus) Human pluripotent stem cell research could also dramatically change the way we develop drugs and test them for safety and efficacy. Rather than evaluating safety and efficacy of a candidate drug in an animal model of a human disease, these drugs could be tested against a human cell line that had been developed to mimic the disease processes. This would not replace whole animal and human testing, but it would streamline the road to discovery. Only the most effective and safest candidate would be likely to graduate to whole animal and then human testing.

There have now been many examples of use of what are called high throughput screens for testing the effect of various chemicals, molecules and drugs on the stem cells and their specialized derivatives. The use of this approach for studies with 'diseased' cells is just beginning as embryonic stem cells have been derived from embryos diagnosed with mutations that can lead to disease later in life.

(Varmus) Perhaps the most far-reaching potential application of human pluripotent stem cells is the generation of cells and tissue that could be used for transplantation, so-called cell therapies. Many diseases and disorders result from disruption of cellular function or destruction of tissues of the body. Today, donated organs and tissues are often used to replace the function of ailing or destroyed tissue. Unfortunately, the number of people suffering from these disorders far outstrips the number of organs available for transplantation. Pluripotent stem cells stimulated to develop into specialized cells offer the possibility of a renewable source of replacement cells and tissue to treat a myriad of diseases, conditions and disabilities including Parkinson's and Alzheimer's disease, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis and rheumatoid arthritis. There is almost no realm of medicine that might not be touched by this innovation

There are now many reports on the use of embryonic stem cell sources of cells for grafting into animals with various injuries or that serve as models for a variety of human diseases. The results have been highly variable (as it has been using stem cells from any source, adult or embryonic) but in many cases, they are encouraging. Our laboratory has been working with cell-based therapies for the heart. Currently there are no adult stem cells that have been identified to date that have shown robust cardiac muscle formation in vivo (in the heart), or for that matter, in vitro (in the dish). We and other laboratories have identified a stem cell that gives rise to most of the cells within the heart and these cells, when grafted to infarcted rodent hearts robustly undergo cardiac muscle formation, integrate into the heart and restore function.

There are three further important points that I want to make in considering the future of providing cures or ameliorating diseases and injuries through stem cell science.

1) Time frame for developing safe and effective therapies.

2) Where disease is involved, we must determine the underlying pathogenesis of the disease and stop it. I have talked only about having a source of cells (or the knowledge of how to control cell fates) in establishing a foundation for future therapies. What is as important, is the understanding of the pathogenesis of devastating diseases for we must stop this process for grafted cells will surely succumb to the same fate.

3) How do the iPS cells factor into the future?
Quite simply I believe that they are important part of the future. They require further vetting as true embryonic stem cells. At the moment, we can only measure what can measure with embryonic stem cells and induced pluripotent stem cells. More must be learned about each. They represent a powerful example of our goal to instruct our cells to do what we want; but this is just the beginning. Is this a farewell to embryonic stem cells in research? Not at all, for they represent the gold standard. For my studies focused on human embryology, I will continue to use embryonic cells but, like many of my colleagues, I will vigorously pursue the direct reprogramming of adult cells.

Summary

Mr. Chairman, I am grateful to you for providing a forum to discuss this promising arena of science and medicine. Learning to instruct our cells to get them to do what we want is the ultimate control of our own cells and the basis of future medicine. Based on current research results with stem cells, the future is, as Yogi Berra has said, not what it used to be. We look to stem cells not only to provide cells for replacements in therapies, but also to provide us with the knowledge of how cells work and to use this information to instruct patients' cells to effect repair and regeneration of damaged or diseased tissues. We must recognize that the development therapies that are safe and effective is going to take time and resources and that circumspection is not a retreat from promise. I would be pleased to answer any questions you might have.